

University of Groningen

Innate immune cells in the placental bed in healthy pregnancy and preeclampsia

Faas, Marijke M; De Vos, Paul

Published in:
Placenta

DOI:
[10.1016/j.placenta.2018.04.012](https://doi.org/10.1016/j.placenta.2018.04.012)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Faas, M. M., & De Vos, P. (2018). Innate immune cells in the placental bed in healthy pregnancy and preeclampsia. *Placenta*, 69, 125-133. <https://doi.org/10.1016/j.placenta.2018.04.012>

Copyright

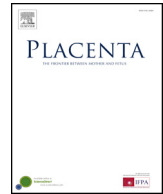
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Innate immune cells in the placental bed in healthy pregnancy and preeclampsia

Marijke M. Faas^{a,b,*}, Paul De Vos^a

^a Immunoenocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

^b Department of Obstetrics and Gynecology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

ARTICLE INFO

Keywords:

Placental bed
Preeclampsia
uNK cells
Macrophages
Dendritic cells
Mast cells
Animal models

ABSTRACT

Immune cells in the placental bed are important for adequate development of the placental bed. The most prominent immune cells in the placental bed early in pregnancy are uterine natural killer cells (uNK) cells and macrophages. Also dendritic cells and mast cells can be found in the early placental bed. These cells not only have an immune regulatory function, but are also involved in the regulation of trophoblast invasion, angiogenesis and spiral artery remodeling. In preeclampsia, one of the major complications of pregnancy, decreased trophoblast invasion and spiral artery remodeling has been found. This is associated with decreased numbers of uNK cells, increased numbers of macrophages around the spiral arteries and similar or increased numbers of dendritic cells in the placental bed. In this review, we discuss the current insights in the functions of uNK cells, macrophages, dendritic cells and mast cells in the placental bed in humans during healthy pregnancy and during preeclampsia. As animal models are instrumental in understanding the role of immune cells in the placental bed, we also review studies on the function and phenotype of these innate immune cells in experimental preeclampsia. A better understanding of the dynamics and functional changes of these immune cells in the placental bed may eventually lead to new therapeutic targets for preeclampsia.

1. Introduction

The human placenta is a hemochorial placenta, which is the most invasive type of placenta. In this placenta there is intimate contact between fetal tissue (trophoblast) and the maternal cells, such as immune cells, at the fetal-maternal interface [1]. Both trophoblast and maternal immune cells are important for proper development of the placental bed, such as spiral artery remodeling, but also for protecting the integrity of the uterus and the mother. The main immune cells present in the placental bed are uterine NK (uNK) cells and macrophages, comprising about 90% of all leukocytes [2]. About 10% of the immune cells are T cells in early human pregnancy [2,3], while dendritic cells, mast cells, granulocytes and B cells can also be found but in lower frequencies [2,4]. A disbalance in immune cell frequencies in the placental bed can lead to disease and pregnancy complications.

Preeclampsia is one of the most important complications in pregnancy, characterized by de novo hypertension accompanied by proteinuria or one or more of the following conditions: renal insufficiency, liver involvement, neurological complications or hematological complications or fetal growth restriction [5]. Preeclampsia can be

subdivided into early onset (onset before 34 weeks) and late onset preeclampsia (onset after 34 weeks). Early onset preeclampsia, which is the most severe form of preeclampsia, is associated with impaired spiral artery remodeling and with changes in the number of trophoblasts and immune cells in the placental bed.

In the present review, we will discuss the current insight on the role of the innate immune cells uNK, macrophages, dendritic cells and mast cells in the placental bed in keeping homeostasis in normal pregnancy and in development of preeclampsia. We will mainly focus on the placental bed in humans, but we will also discuss some relevant rodent models that have contributed to the current knowledge on the function of innate immune cells in the placental bed of healthy pregnancy or preeclampsia.

2. Uterine NK cells in the human placental bed

2.1. Healthy pregnancy

NK cells are classified as lymphocytes, with cytotoxic and cytokine producing functions [6]. They are characterized by CD56 expression

* Corresponding author. Immunoenocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University Medical Center Groningen, Hanzplein 1, 9713 GZ, Groningen, The Netherlands.

E-mail address: m.m.faas@umcg.nl (M.M. Faas).

<https://doi.org/10.1016/j.placenta.2018.04.012>

Received 30 November 2017; Received in revised form 23 March 2018; Accepted 23 April 2018

0143-4004/ © 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

(NK cell marker) and lack of expression of CD3 (T cell marker) [6]. In humans, two populations of NK cells can be distinguished: the cytotoxic NK cells, (CD56 + /CD16 +) (CD16 is the low affinity Fc receptor), representing about 90% of all NK cells and the cytokine producing NK cells, (CD56 + + /CD16 -), which are also known as regulatory NK cells [6]. Although uNK cells in the human endometrium and placental bed do express high levels of CD56 and lack CD16 expression, in contrast to the circulating cells, they are granulated and express different markers [2]. For instance, they express higher levels of Killer-cell immunoglobulin-like receptors (KIR) and natural killer group (NKG) 2 A/C/E/D [7] as compared with blood NK cells. Both these receptors can bind to Human Leukocyte Antigen (HLA) C and E expressed by the trophoblast [7]. uNK cells, in contrast to blood NK cells, express CD9, involved in cell adhesion and motility, and CD49a, involved in cell adhesion [7,8].

uNK cell-receptors, KIRs, are important for the function of uNK cells. The expression of these receptors seems to be regulated by oxygen tension in the decidua [9]. KIR receptors bind to Human Leukocyte antigen molecules (HLA) molecules on trophoblast and this binding is important for uNK cell function, for instance for the production of certain growth factors [10]. The binding of uNK cell KIR receptors to trophoblast HLA molecules is also important for trophoblast migration and spiral artery remodeling [10]. The expression of certain KIR receptors (activating KIR receptors), such as KIR2DS1 [10], KIR2DS4 [11] and KIR2DS5 [12] in combination with extravillous trophoblast expression of HLA-C2 is important for normal trophoblast invasion and spiral artery remodeling and therefore for normal placental development.

In the placental bed of early human pregnancy, the numbers of uNK increase [3,13]. After the first trimester, the numbers of uNK cells decrease in the placental bed [14], but they are still present at the end of pregnancy [15,16]. In healthy pregnancy, uNK cells are usually found in the vicinity of invading fetal trophoblast cells [17], and around spiral arteries, that are being remodeled [18]. The potential role of these cells in trophoblast invasion has been shown by *in vitro* studies. Conditioned medium from uNK cells have been shown to increase chemoattraction of trophoblasts [19,20]. Chemotactic promoting factors may be hepatocyte growth factor [21], IL-8, CXCL10 [22] or IL-6 [23] or protease activity [24]. Interferon γ (IFN γ), on the other hand, may decrease trophoblast migration [25].

Spiral artery remodeling takes place in 2 phases: in the first phase, there is a loss of the musculo-elastic structure and the formation of endothelial cell layer breaks [18]. In the second phase, endovascular trophoblasts are attracted towards the spiral arteries and replace the endothelial lining in the decidua and first part of the myometrium [18]. uNK cells play a role in both phases of spiral artery remodeling [18,26,27]. The mechanism by which uNK cells affect spiral artery remodeling is not exactly clear, however, uNK cells produce many factors, such as cytokines (for instance Tumor necrosis factor- α (TNF α), interleukin-10), growth factors (for instance Macrophage colony-stimulating factor (M-CSF), Placental growth factor (PlGF)), angiogenic factors (such as Vascular endothelial growth factor-C (VEGF-C) Angiopoietin 2 (Ang2)), and other factors, like matrix metalloproteinases (MMPs) [27–31]. These factors play a role in spiral artery remodeling [27,28,32].

2.2. Preeclampsia

As already outlined in the introduction, preeclampsia is one of the most important complications of pregnancy, characterized by hypertension in combination with proteinuria, renal insufficiency, liver involvement, neurological complications or hematological complications or fetal growth restriction [5]. Preeclampsia can be divided into early onset (onset before 34 weeks) and late onset preeclampsia (onset after 34 weeks). The early onset form of preeclampsia is associated with decreased trophoblast invasion and spiral artery remodeling as well as

with fetal growth restriction [33], resulting in a stressed placenta. The stressed placenta then starts secreting various inflammatory, anti-angiogenic and other damaging factors into the maternal circulation resulting in a generalized maternal inflammatory response and endothelial cell dysfunction and finally preeclampsia [33].

Changes in uNK cells numbers in the placental bed have been found in preeclamptic patients. However, some studies found increased numbers of uNK cells in decidua from women with preeclampsia compared with age matched controls [34–36], while others have demonstrated decreased numbers of uNK cells in placental bed biopsies of preeclamptic patients [37,38] or observed no difference [15]. Differences in these studies may be due to for instance the use of different experimental methods or the use of tissue from preeclamptic patients, which differed in severity (f.i. preeclampsia with or without growth restriction) or the fact that different placental bed locations were studied (f.i. uNK close to spiral arteries or total numbers of uNK cells in the placental bed). It seems that total numbers of uNK cells are correlated to the presence of fetal growth restriction (FGR), rather than to preeclampsia itself, since the total numbers of uNK cells seems to be decreased in pregnancies with FGR (with or without preeclampsia) [37,38] and correlated with decreased spiral artery remodeling [38].

As indicated above, the expression of certain KIR receptors (i.e. activating KIR receptors such as KIR2DS1, KIR2DS4 and KIR2DS5) is important for normal development of the placental bed and thus normal pregnancy [10–12]. This suggests that a lack of expression of these receptors or expression of other KIR receptors may be associated with deficient trophoblast invasion and spiral artery remodeling. Indeed, women with mainly inhibitory KIR receptors (KIR AA genotype) (such as KIR2DL1, KIR2DL2, KIR2DL5 and KIR3DL3) in combination with trophoblast expression of HLA-C2 have an increased the risk for developing preeclampsia [39].

Unfortunately, studying uNK cells in biopsies taken from decidua or placental bed after parturition are not informative for the pathophysiology of preeclampsia. Changes found in uNK cells in these biopsies may be the result or the cause of preeclampsia. Therefore, biopsies at the time of trophoblast invasion and spiral artery remodeling are needed. However, collection of placental bed tissue from this time of pregnancy is limited to tissue obtained from termination of pregnancy. The disadvantage of this tissue is that no information is available as to the outcome of the pregnancy. The group of Whitley and Cartwright, however, has developed a strategy to overcome this problem. They have used uterine artery Doppler ultrasound screening to identify women at increased risk for developing preeclampsia and growth restriction, i.e. women with a high uterine artery resistance index i.e. a resistance index of > 95th percentile [40]. Using uNK cells isolated from women with a high resistance index as indicated by uterine artery Doppler screening and from women with a normal resistance index showed that uNK cells from women with a high resistance index were less able to promote invasive behavior of trophoblast *in vitro* as compared to women with normal resistance index [21]. This may be due to a decreased expression of various uNK cells receptors, such as KIR2DL1/S1 receptors and LILRB1 receptors in women with a high resistance index [41]. This may result in impaired trophoblast-uNK cell interactions [19,41] and differences in secreted factors between uNK cells in women with a high resistance index as compared with women with a normal resistance index [41]. In line with the different functions of uNK cells from women with a high resistance index, uNK cells from these women induced increased endothelial cell activation, destabilized endothelial tube like structures and induced more TNF α production by endothelial cells as compared to uNK cells from women with a normal resistance index [42]. These data suggest that there are changes in uNK cells function in women who later develop preeclampsia during the time of trophoblast invasion and spiral artery remodeling, suggesting that changes in uNK cell function may play a role in the pathophysiology of early onset preeclampsia.

3. Uterine NK cells in rodent placental bed

3.1. Healthy pregnancy

A lot of knowledge on the role of uNK cells in spiral artery remodeling in healthy pregnancy is derived from mice studies. Similar to humans, uNK cells in the mouse are activated [43] and express cytokines, such as IFN γ and IL-22 [44,45], as well as growth factors, such as and PLGF [45] and angiogenic factors, such as VEGF [46]. Mouse uNK cells also express the mouse equivalent of the KIR receptors, i.e. LY49 [47].

In the mouse, uNK cells play a major role in spiral artery remodeling, since NK cell deficient mice largely lack spiral artery remodeling and have abnormal decidual and myometrial structures at mid gestation [48]. The role of uNK cells is even more apparent for experiments in which NK cells were reconstituted in NK cell deficient mice, which recovered spiral artery remodeling [49]. However, also IFN γ administration to NK cell deficient mice resulted in recovery of spiral artery remodeling [44], suggesting that IFN γ is important for spiral artery remodeling. IFN γ may provide the initiating step in spiral artery modification [44]. Also other factors may affect spiral artery remodeling in the mouse, such as nitric oxide [50] or angiogenic factors, such as VEGF [51].

As the mouse is not an adequate model for deep trophoblast invasion, rat models are used to study deep trophoblast invasion and the interaction between uNK cells and trophoblast invasion [52,53]. Staining of uNK cells and trophoblast in consecutive sections of the mesometrial triangle, which is the equivalent of the human placental bed, on days 15, 17 and 20 of rat pregnancy showed that extravillous trophoblast invasion followed the demise of uNK cells in the direction of the myometrium, suggesting that uNK cells regulate extravillous trophoblast invasion [54]. uNK cells may also regulate endovascular trophoblast invasion, since depletion of NK cells in early pregnancy, resulted in increased endovascular trophoblast invasion at day 13 [55].

Chakraborty et al. [55] have shown that uNK cells promote uterine spiral artery growth towards the ectoplacental cone [55] and that uNK cells cause a partial disruption of the spiral artery tunica media integrity [55]. We showed that uNK cells, but not interstitial or endovascular trophoblasts, were found in the presence of partly remodeled spiral arteries in the mesometrial triangle of day 15 of pregnancy [54].

3.2. Preeclampsia

Both mice and rats models are instrumental in understanding the pathophysiology and role of uNK cells in preeclampsia. Mice and rat models for preeclampsia allow studying uNK cells at different time points of pregnancy. One study has shown that in a mouse model for preeclampsia uNK cells are decreased in the mesometrial triangle in mid gestation and that this lower presence of these cells correlated with decreased spiral artery remodeling [56]. A study from our own lab demonstrated that in a rat model for preeclampsia, decreased trophoblast invasion and spiral artery remodeling was associated with decreased numbers of uNK cells [52]. In contrast to depletion of NK cells in healthy pregnant rats, depletion of NK cells in a preeclamptic rat model (female human angiotensinogen \times male human renin) reduced trophoblast invasion, with no effect on spiral artery remodeling [57]. In line with studies on the function of uNK cells in humans, these studies therefore also show that the numbers of uNK cells are decreased in preeclampsia and that the function of uNK cells may have changed in preeclampsia; while in normal pregnancy uNK cells inhibit trophoblast invasion, in preeclampsia they may promote trophoblast invasion. Further studies into uNK cell function in preeclampsia and in models for preeclampsia are needed.

4. Macrophages in the human placental bed

4.1. Healthy pregnancy

Macrophages are important for the detection, ingestion and processing of foreign material, dead cells and cell debris [58]. Various subsets of macrophages have been described, with M1 (classically activated macrophages) and M2 (alternatively activated macrophages) macrophages at the extreme ends [59,60]. M1 macrophages are microbicidal and proinflammatory, M2 macrophages are immunomodulatory, inducing tolerance and resolution of inflammation [59].

Macrophages are present in the placental bed at all times during pregnancy [61], comprising 20–30% of all decidual leukocytes in early pregnancy [62]. The number of placental bed macrophages decreases with advancing gestational age [37]. Placental bed macrophages are mainly of the M2 subset [16,63–67] and produce many factors, such as factors associated with immunomodulation, such as the cytokines IL-4, IL-10, TNF α , factors associated with angiogenesis (for instance angiogenin or VEGF) and proteases (MMPs) [68–70]. However, they may not be typical M2 macrophages, since they are not typically induced by Th2 cytokines, but by M-CSF and IL-10 [71]. Macrophages can be found near spiral arteries that are in the process of early remodeling, i.e. spiral arteries in the absence of extravillous trophoblast [18]. This may suggest that macrophages prepare spiral arteries for further remodeling by trophoblast cells. Macrophages around the spiral arteries may also engulf apoptotic cells, formed during remodeling, and thereby preventing the release of proinflammatory substances into the decidua [72,73].

4.2. Preeclampsia

Studies on macrophages in the placental bed in preeclampsia have mainly been done on placental bed tissue after parturition. Some of these studies reported decreased numbers of macrophages in the decidua of preeclamptic patients [37,74]. However, various other studies have reported increased numbers of macrophages in the placental bed of preeclamptic patients [67,75,76]. Differences between studies may be due to for instance different methods used (flow cytometric study vs immunohistochemical studies), different antibodies used or different locations in the placental bed being studied. This latter is especially important, since differences in macrophage numbers seem to be regional, as increased numbers of macrophages were found around the spiral arteries of preeclamptic patients but not necessarily at other sites [77]. This increased numbers of macrophages around the spiral arteries may be due to an increased presence of chemotactic factors for macrophages [77–79] found in the placental bed of preeclamptic patients as compared with the placental bed of healthy control women.

Not only numbers of macrophages were different in preeclamptic patients, macrophages were also differently activated in preeclampsia [77,79–82]. Recent *in vitro* studies showed that macrophages migrate towards invading trophoblast [83], while other groups have shown that activated macrophages *in vitro* are able to inhibit trophoblast invasion and spiral artery remodeling [84,85]. Therefore, the presence of activated macrophages may play a role in the decreased trophoblast invasion and spiral artery remodeling in preeclampsia.

The different activation status of placental bed macrophages in preeclampsia may be related to a decreased number of M2 macrophages and an increased number of M1 macrophages in the placental bed of preeclamptic women [67]. This is in concordance with increased proinflammatory [86] and decreased anti-inflammatory cytokines in the placenta of preeclamptic women [87,88]. The polarization state of the macrophages may be important for their function in the placental bed, since conditioned medium of M1 macrophages inhibited trophoblast motility and trophoblast tube formation as compared with conditioned medium from M2 macrophages [89].

It is unknown whether the increased numbers and different

activational state of macrophages in the placental bed of preeclamptic women is the cause or the consequence of preeclampsia. We have tried to shed light on this question by studying expression of immunological genes in early decidua from women who later developed pregnancy-induced hypertension (PIH; including preeclampsia). We observed that in the early decidua CD68 mRNA expression (a general macrophage marker) was increased and the CD206/CD68 mRNA ratio (CD206 is a marker for M2 macrophages) was decreased in women who later developed pregnancy induced hypertension (including preeclampsia) [90]. These data indicate that the increased numbers of M1 macrophages and decreased numbers of M2 macrophages may already be present before the onset preeclampsia and thus that macrophages may indeed play a role in the pathophysiology of preeclampsia.

5. Macrophages in rodent placental bed

5.1. Healthy pregnancy

In both mice and rats, macrophages are present in the placental bed, both in the decidua and the myometrium [52,91,92]. They are found scattered throughout the mesometrial triangle and also around the spiral arteries, but with no apparent relation with remodeling [52,93]. At the end of pregnancy, macrophages are the largest population of immune cells in the mesometrial triangle [52,94]. In the rat, we found only a few M2 macrophages in the mesometrial triangle of healthy pregnant rats at the end of pregnancy [52]. It remains to be shown whether macrophages have a role in spiral artery remodeling in the mesometrial triangle in rats and mice.

5.2. Preeclampsia

In an animal model for preeclampsia induced by multiple doses of LPS in pregnant rats, decreased trophoblast invasion and spiral artery remodeling after LPS was associated with increased numbers of CD68 positive macrophages [95]. In a different model for preeclampsia (ATP infusion), we found no differences in total macrophages in the mesometrial triangle between control and ATP infused pregnant rats [52], however, numbers of activated macrophages were increased 1 day after ATP infusion, suggesting that activated macrophages may play a role in the pathophysiology of preeclampsia in this model [52]. Further studies into the role of macrophages in the placental bed in animal models may shed more light on the function of macrophages in the placental bed in human pregnancy and preeclampsia.

6. Dendritic cells in the human placental bed

6.1. Healthy pregnancy

Dendritic cells are innate immune cells. They are antigen presenting cells, which are major players in adaptive immune responses. They capture antigen in the periphery, after which they migrate to the lymph nodes, where they present the antigen to T cells. This results in an expansion and polarization of T cells and finally in an antigen specific immune response [96]. Dendritic cells are present in the cycling endometrium and in the placental bed [97]. The number of dendritic cells decrease in early pregnancy as compared with the non-pregnant endometrium [98]. The numbers of dendritic cells are low in the early placental bed, much lower than the number of macrophages [99], and the dendritic cells appear to be scattered throughout the placental bed [100]. Although, both mature (CD83⁺) and immature dendritic cells (DC-SIGN positive) are found in the placental bed, the number of immature dendritic cells is much higher than the number of mature dendritic cells [99]. This may be due to the production of factors by decidual stromal cells inhibiting maturation of dendritic cells in the placental bed [101]. Thus, most dendritic cells appear to be in a resting immature state, which main function is to maintain immune tolerance

[96]. This suggestion is in line with the finding in *in vitro* studies, which suggested that dendritic cells may play a role in skewing immune responses towards Th2 type responses [102]. Moreover, a population of CD14 + DC-SIGN positive dendritic cells, which is only present in the pregnant placental bed and not in the non-pregnant endometrium, has been shown to be able to induce Tregs *in vitro*, suggesting that this population of placental bed dendritic cells may also induce Treg cells in the placental bed [103].

In the human placental bed, DCs seem to closely interact with uNK cells, since DC-SIGN positive dendritic cells were found to have close contact with CD56 + CD16-uNK cells [99]. This suggests close collaboration between uNK cells and DC cells, which is in line with the close collaboration between NK cells and dendritic cells in other tissues [104]. There is indeed evidence of close collaboration of uterine DCs and NK cells from *in vitro* studies that show enhanced proliferation and activation of NK cells after coculture with decidual DCs [105], while human DCs improve their ability to induce Treg after interaction with uNK cells [106].

6.2. Preeclampsia

Only a few studies have evaluated dendritic cells in the placental bed in preeclampsia. Current studies show that the total numbers of dendritic cells in the placental bed may be similar or higher in the placental bed of preeclamptic women [103,107]. The proportion of mature dendritic cells was significantly higher in the decidua of preeclamptic patients as compared with healthy pregnant women [108]. This may suggest activation of dendritic cells in the preeclamptic placental bed, which may result in activation of Th1 cells and inflammation in the placental bed [108]. Although the population of CD14 + DC-SIGN positive dendritic cells, as described by Hsu [103], did not change in preeclamptic pregnancies, these cells from the preeclamptic placental bed were less able to induce regulatory T cells [103].

7. Dendritic cells in rodent placental bed

7.1. Healthy pregnancy

Mouse models have been instrumental in evaluating the role of DC cells in the placental bed. Similar to the human uterus, also in the mouse uterus, DC are present in the non-pregnant state. Highest DC numbers can be found during the estrus phase of the ovarian cycle [109,110]. Decidual dendritic cells were lower in the decidua as compared with the non-pregnant uterus in mice [111]. DC function is inhibited by the decidua and therefore placental bed DCs do not contribute to an anti-fetal/placental T cell response [111] [112]. However, the dendritic cells do have an immunomodulatory role, which was for instance shown by a study in the abortion prone mouse mating CBA/J x DBA/2J [113]. In the placental bed of these abortion prone mothers, the number of DC is decreased. However, adoptive transfer of syngeneic DCs in these mothers, decreased the number of fetal resorptions [113], by inducing pregnancy protective CD8 and $\gamma\delta$ cell populations as well as increased expression of the tolerogenic TGF- β [113].

Apart from the immunomodulatory role of placental bed DCs, mouse models have shown that DCs are also important in the development of the placental bed. Depletion of DCs in early pregnancy in mice, resulted in decreased size of the implantation sites [114]. These mice also showed signs of fetal resorption [114] and an inhibited development of the decidua. This is associated with impaired expansion of the decidual vascular bed together with decreased vessel permeability and blood flow [115,116]. These data are in line with the suggestion that DCs play an important role in angiogenesis in the placental bed [117].

Increased numbers of DCs at the implantation sites did not affect the implantation size or induced fetal resorptions [114]. However, depletion of uNK cells in the presence of increased numbers of DCs, led to

decreased implantation sizes and complete pregnancy failure [114]. Also exogenous administration of IL-10 in mice with increased numbers of DC and depleted NK cells, rescued pregnancy, indicating that IL-10 production by uNK cells, may be important in the NK-DC dialog in early pregnancy [118]. These results suggest that, in accordance with human studies showing *in vitro* interaction DCs with uNK in the placental bed cells, indeed, *in vivo* uNK cells and DCs closely collaborate. This dialog between placental bed DC and uNK is not only important for immune regulation in the placental bed, but also for decidual angiogenesis [117]. Moreover, *in vitro* studies have shown that the dialog between DC and NK cells also affected uterine cell proliferation induced by trophoblast cells [119]. This could have implications for endometrial decidualization in early pregnancy.

8. Mast cells in the human placental bed

8.1. Healthy pregnancy

Mast cells are innate immune cells that circulate in the blood in an immature form and migrate to the tissues, such as mucosal tissues, amongst which the placental bed, in which they mature under the influence of various factors, such as factors from the environment. This indicates that mast cells may mature differently in different tissues [120]. Indeed, mast cells in the decidua differ from mast cells in other tissues [121].

Mast cells are present in the endometrium of non-pregnant women, with no differences in numbers of mast cells between the follicular phase and the luteal phase of the ovarian cycle [122,123]. However, premenstrually, mast cells seem to be activated [122]. Mast cells are also present in the uterus during pregnancy [124]. The density of mast cells was higher in the pregnant uterus as compared to the non-pregnant uterus [125]. In the placental bed, mast cells were not only closely located to decidual extra villous trophoblast, they also seem to interact with these cells [126]. *In vitro* studies have shown that conditioned medium from mast cells increased trophoblast migration [126], suggesting a role for mast cells in trophoblast invasion in the placental bed.

8.2. Preeclampsia

A few studies evaluated mast cell numbers in the placenta in preeclamptic patients [127–129]. Presence of mast cells was studied in the villous part of the placenta with conflicting results. While two studies found increased numbers of mast cells in the villous part of the placenta [127,129], the other study [128] found decreased numbers of mast cells in the villous part of the placenta in preeclamptic women as compared with healthy pregnant women. However, to the best of our knowledge, no studies have looked at mast cells in the preeclamptic placental bed.

9. Mast cells in the rodent placental bed

9.1. Healthy pregnancy

Most of knowledge on the role of mast cells in development of the placental bed arises from mice studies. In the mouse, mast cells are already present in the non-pregnant uterus, with numbers peaking at estrus [130] and an increase in number during early pregnancy [130,131]. In abortion prone mice, numbers of mast cells do not increase during early pregnancy [130], suggesting a role for these cells in early healthy pregnancy. Since adoptive transfer of Tregs in these mice increased the numbers of mast cells in the placental bed and rescued pregnancy, Tregs seem to regulate the number of mast cells in the placental bed [130]. The role of mast cells in early pregnancy is further shown by studies in mast cell deficient mice. These studies have shown that mast cells indeed play a role in early pregnancy, mainly in implantation and placentalation. Studies in mouse deficient for mast cells, showed a diminished size of the implantation site as compared with

control mice with sufficient mast cells [131], while the transfer of bone marrow derived mast cells into mast cell deficient mice restored the size of the implantation sites [131]. Mast cell deficiency in pregnant mice also resulted in decreased spiral artery remodeling, fetal growth restriction [126] and decreased placental size [131]. Mast cells may also play a role in angiogenesis, since degranulation of mast cells induced angiogenesis in the cervix [132,133].

Like dendritic cells, also mast cells seem to interact with uNK cells. Mice deficient in either mast cells or NK cells show impairment in spiral artery remodeling as well as fetal growth retardation [134]. Mice deficient in both mast cells and NK cells show a much more marked impairment in spiral artery remodeling and fetal growth restriction [135]. Together with the observation that mice deficient in mast cells show increased numbers of uNK cells in the placental bed, while mice deficient for uNK cells show increased numbers of mast cells at the implantation site [134], this suggests the both cell types jointly affect placental bed development in early pregnancy and counterbalance each other.

10. Concluding remarks

Important advances have been made in understanding the role of innate immune cells, such as uNK, macrophages, dendritic cells and mast cells in the placental bed of healthy and preeclamptic pregnancies (Fig. 1). These innate immune cells are important for normal development of the placental bed. Since these cells are often found in the vicinity of invading extravillous trophoblast as well as of spiral arteries, they seem to play a role in trophoblast invasion and spiral artery remodeling. This is also apparent from the fact that decreased numbers of uNK cells are found in association with decreased spiral artery remodeling and increased numbers of macrophages are found around the spiral arteries in preeclampsia. Although there is no consensus on the numbers of dendritic cells in the placental bed in preeclampsia, the number of mature dendritic cells are increased, which may be associated with a different immune regulation, such as increased inflammation and numbers of Th1 cells. Unfortunately, no data are available on mast cells in preeclampsia. In healthy pregnant women, the innate immune cells mainly have a regulatory phenotype (i.e. producing regulatory factors, such as regulatory cytokines, growth factors, angiogenic factors and factors associated with tissue remodeling) (Fig. 1, left panel). In preeclampsia, innate immune cells seem to have a more proinflammatory phenotype. This results in production of different factors, such as increased production of proinflammatory cytokines and decreased production of tissue remodeling factors (Fig. 1, right panel). These changes in preeclampsia may result in decreased spiral artery remodeling and decreased trophoblast invasion. The role of dendritic cells and mast cells needs further investigation.

More studies on the exact role and timing of presence of innate immune cells in the placental bed are needed. Especially the role of dendritic cells and mast cells and the interaction between the different innate immune cells in the placental bed needs further investigation.

As human placental bed tissue samples at the time of trophoblast invasions and spiral artery remodeling are very difficult to collect, studies into these cells should take better advantage of animal models. Relatively low numbers of studies on the role of uNK cells and uterine macrophages in preeclampsia are performed in rat and mouse models, despite the fact that these cells seem to have functions similar to human uNK cells and uterine macrophages. No studies on mast cells and dendritic cells have been performed in animal models for preeclampsia. Studies on innate immune cells during the course of healthy pregnancy and experimental preeclampsia in mice and rats could lead to better insight into the function and dysfunction of these cells during pregnancy and preeclampsia in humans and eventually to novel targets for treatment of preeclampsia.

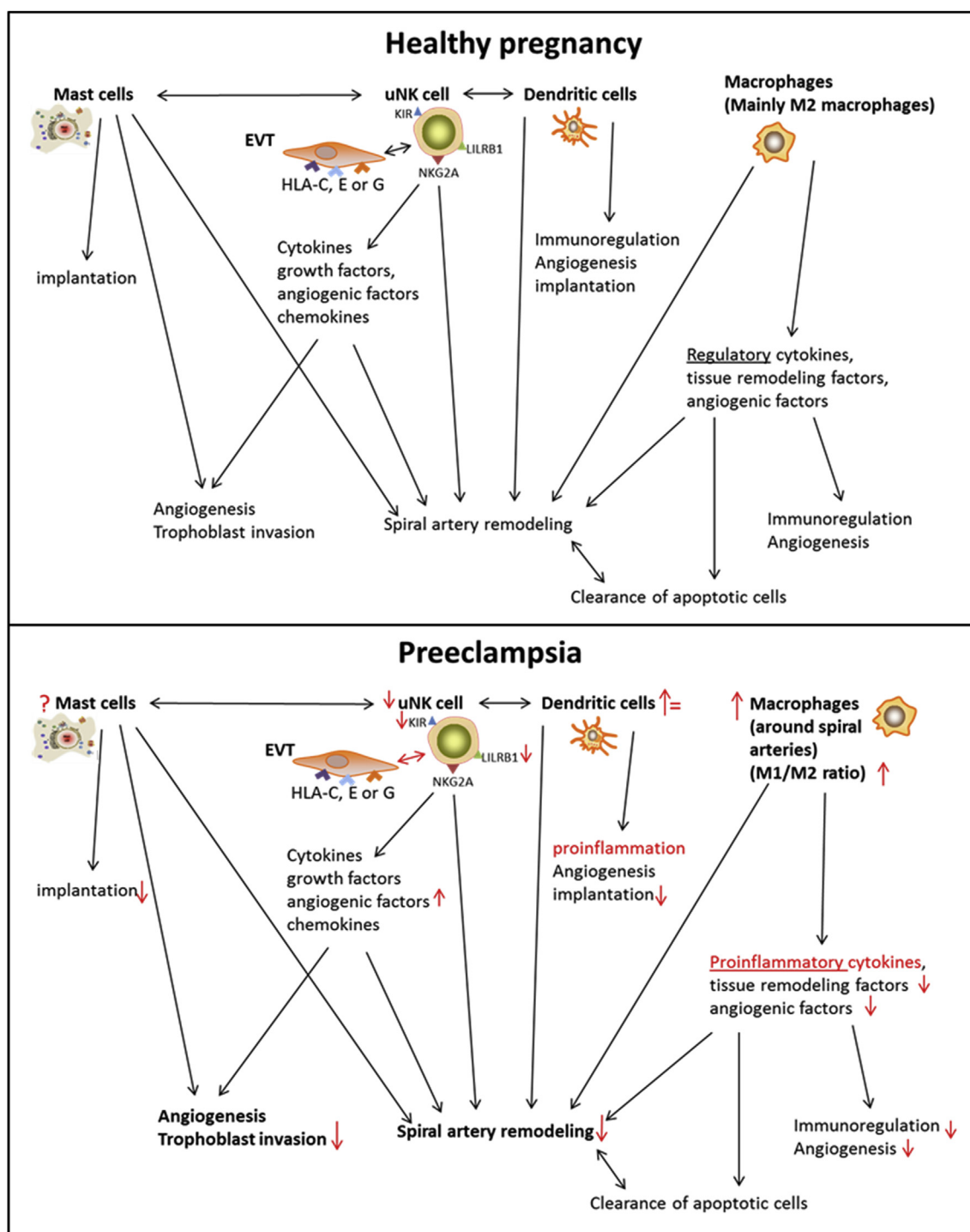


Fig. 1. The function of uNK cells, macrophages, dendritic cells and mast cells in the placental bed in normal pregnancy and preeclampsia. In normal pregnancy (top panel), the innate immune cells are involved in spiral artery remodeling and production of cytokines and other factors in the placental bed. uNK cell function may depend on binding of their inhibitory and activating receptors to HLA on extravillous trophoblast (EVT). All innate immune cell types also have other functions in the decidua, such as angiogenesis and immunoregulation but they may also play a role in implantation. In preeclampsia (lower panel) uNK cell, macrophage and dendritic cells function and numbers may have changed, while no data are available on mast cells. Numbers and expression of some KIR receptor on uNK decreased and numbers of macrophages (around the spiral arteries), especially type M1 macrophages, increased. This results in different expression of various factors and finally may result in decreased trophoblast invasion and spiral artery remodeling as well as decreased angiogenesis, immunoregulation and implantation. (adapted from Faas et al., Placenta, 2017: 56:44–52).

Conflicts of interest

We have no conflict of interest.

References

- [1] E.N.T. Meeusen, R.J. Bischof, C.S. Lee, Comparative T-cell responses during pregnancy in large animals and humans, *Am. J. Reprod. Immunol.* 46 (2001) 169–179.
- [2] A. Trundley, A. Moffett, Human uterine leukocytes and pregnancy, *Tissue*

- Antigens 63 (1) (2004) 1–12.
- [3] A. King, V. Wellings, L. Gardner, Y.W. Loke, Immunocytochemical characterization of the unusual large granular lymphocytes in human endometrium throughout the menstrual cycle, *Hum. Immunol.* 24 (1989) 195–205.
 - [4] J.N. Bulmer, P.M. Johnson, Macrophage populations in the human placenta and amniochorion, *Clin Exp Immunol* 57 (2) (1984) 393–403.
 - [5] A.L. Tranquilli, G. Dekker, L. Magee, J. Roberts, B.M. Sibai, W. Steyn, G.G. Zeeman, M.A. Brown, The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP, *Pregnancy hypertension* 4 (2) (2014) 97–104.
 - [6] E. Vivier, E. Tomasello, M. Baratin, T. Walzer, S. Ugolini, Functions of natural killer cells, *Nat. Immunol.* 9 (5) (2008) 503–510.
 - [7] L.A. Koopman, H.D. Kopcow, B. Rybalov, J.E. Boyson, J.S. Orange, F. Schatz, R. Masch, C.J. Lockwood, A.D. Schachter, P.J. Park, J.L. Strominger, Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential, *J. Exp. Med.* 198 (8) (2003) 1201–1212.
 - [8] J. Dietl, P. Ruck, K. Marzusch, H.P. Horny, E. Kaiserling, R. Handgretinger, Uterine granular lymphocytes are activated natural killer cells expressing VLA-1, *Immunol. Today* 13 (6) (1992) 236.
 - [9] A.E. Wallace, S.S. Goulwara, G.S. Whitley, J.E. Cartwright, Oxygen modulates human decidual natural killer cell surface receptor expression and interactions with trophoblasts, *Biol. Reprod.* 91 (6) (2014) 134.
 - [10] S. Xiong, A.M. Sharkey, P.R. Kennedy, L. Gardner, L.E. Farrell, O. Chazara, J. Bauer, S.E. Hiby, F. Colucci, A. Moffett, Maternal uterine NK cell-activating receptor KIR2DS1 enhances placentation, *J. Clin. Invest.* 123 (10) (2013) 4264–4272.
 - [11] P.R. Kennedy, O. Chazara, L. Gardner, M.A. Ivarsson, L.E. Farrell, S. Xiong, S.E. Hiby, F. Colucci, A.M. Sharkey, A. Moffett, Activating KIR2DS4 is expressed by uterine NK cells and contributes to successful pregnancy, *J. Immunol.* 197 (11) (2016) 4292–4300.
 - [12] A. Nakimuli, O. Chazara, S.E. Hiby, L. Farrell, S. Tukwasibwe, J. Jayaraman, J.A. Traherne, J. Trowsdale, F. Colucci, E. Lougee, R.W. Vaughan, A.M. Elliott, J. Byamugisha, P. Kaleebu, F. Mirembe, N. Nemat-Gorgani, P. Parham, P.J. Norman, A. Moffett, A KIR B centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia, *Proc. Natl. Acad. Sci. U.S.A.* 112 (3) (2015) 845–850.
 - [13] J.N. Bulmer, L. Morrison, M. Longfellow, A. Ritson, D. Pace, Granulated lymphocytes in human endometrium: histochemical and immunohistochemical studies, *Hum. Reprod.* 6 (6) (1991) 791–798.
 - [14] A. Moffett-King, Natural killer cells and pregnancy, *Nat. Rev. Immunol.* 2 (9) (2002) 656–663.
 - [15] L. Rieger, S. Segerer, T. Bernar, M. Kapp, M. Majic, A.K. Morr, J. Dietl, U. Kammerer, Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia—a prospective observational study, *Reprod. Biol. Endocrinol.: RBE (Rev. Bras. Entomol.)* 7 (2009) 132.
 - [16] P.J. Williams, R.F. Searle, S.C. Robson, B.A. Innes, J.N. Bulmer, Decidual leucocyte populations in early to late gestation normal human pregnancy, *J. Reprod. Immunol.* 82 (1) (2009) 24–31.
 - [17] C. Helige, H. Ahammer, G. Moser, A. Hammer, G. Dohr, B. Huppertz, P. Sedlmayr, Distribution of decidual natural killer cells and macrophages in the neighbourhood of the trophoblast invasion front: a quantitative evaluation, *Hum. Reprod.* 29 (1) (2014) 8–17.
 - [18] S.D. Smith, C.E. Dunk, J.D. Aplin, L.K. Harris, R.L. Jones, Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy, *Am. J. Pathol.* 174 (5) (2009) 1959–1971.
 - [19] A.E. Wallace, A.J. Host, G.S. Whitley, J.E. Cartwright, Decidual natural killer cell interactions with trophoblasts are impaired in pregnancies at increased risk of preeclampsia, *Am. J. Pathol.* 183 (6) (2013) 1853–1861.
 - [20] G.E. Lash, H.A. Otun, B.A. Innes, K. Percival, R.F. Searle, S.C. Robson, J.N. Bulmer, Regulation of extravillous trophoblast invasion by uterine natural killer cells is dependent on gestational age, *Hum. Reprod.* 25 (5) (2010) 1137–1145.
 - [21] R. Fraser, G.S. Whitley, A.P. Johnstone, A.J. Host, N.J. Sebire, B. Thilaganathan, J.E. Cartwright, Impaired decidual natural killer cell regulation of vascular remodeling in early human pregnancies with high uterine artery resistance, *J. Pathol.* 228 (3) (2012) 322–332.
 - [22] J. Hanna, D. Goldman-Wohl, Y. Hamani, I. Avraham, C. Greenfield, S. Natanson-Yaron, D. Prus, L. Cohen-Daniel, T.I. Arnon, I. Manaster, R. Gazit, V. Yutkin, D. Benharroch, A. Porgador, E. Keshet, S. Yagel, O. Mandelboim, Decidual NK cells regulate key developmental processes at the human fetal-maternal interface, *Nat. Med.* 12 (9) (2006) 1065–1074.
 - [23] M. Jovanovic, L. Vicoval, Interleukin-6 stimulates cell migration, invasion and integrin expression in HTR-8/SVneo cell line, *Placenta* 30 (4) (2009) 320–328.
 - [24] K. Naruse, G.E. Lash, J.N. Bulmer, B.A. Innes, H.A. Otun, R.F. Searle, S.C. Robson, The urokinase plasminogen activator (uPA) system in uterine natural killer cells in the placental bed during early pregnancy, *Placenta* 30 (5) (2009) 398–404.
 - [25] Y. Hu, J.P. Dutz, C.D. MacCalman, P. Yong, R. Tan, P. von Dadelszen, Decidual NK cells alter in vitro first trimester extravillous cytotrophoblast migration: a role for IFN- γ , *J. Immunol.* 177 (12) (2006) 8522–8530.
 - [26] L.K. Harris, Review: trophoblast-vascular cell interactions in early pregnancy: how to remodel a vessel, *Placenta* 31 (Suppl) (2010) S93–S98.
 - [27] A. Robson, L.K. Harris, B.A. Innes, G.E. Lash, M.M. Aljunaidy, J.D. Aplin, P.N. Baker, S.C. Robson, J.N. Bulmer, Uterine natural killer cells initiate spiral artery remodeling in human pregnancy, *Faseb. J.* 26 (12) (2012) 4876–4885.
 - [28] G.E. Lash, B. Schiessl, M. Kirkley, B.A. Innes, A. Cooper, R.F. Searle, S.C. Robson, J.N. Bulmer, Expression of angiogenic growth factors by uterine natural killer cells during early pregnancy, *J. Leukoc. Biol.* 80 (3) (2006) 572–580.
 - [29] P.P. Jokhi, A. King, Y.W. Loke, Production of granulocyte-macrophage colony-stimulating factor by human trophoblast cells and by decidual large granular lymphocytes, *Hum. Reprod.* 9 (9) (1994) 1660–1669.
 - [30] S. Saito, K. Nishikawa, T. Morii, M. Enomoto, N. Narita, K. Motoyoshi, M. Ichijo, Cytokine production by CD16-CD56bright natural killer cells in the human early pregnancy decidua, *Int. Immunol.* 5 (5) (1993) 559–563.
 - [31] K. Naruse, G.E. Lash, B.A. Innes, H.A. Otun, R.F. Searle, S.C. Robson, J.N. Bulmer, Localization of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitors for MMPs (TIMPs) in uterine natural killer cells in early human pregnancy, *Hum. Reprod.* 24 (3) (2009) 553–561.
 - [32] M.A. Moses, The regulation of neovascularization of matrix metalloproteinases and their inhibitors, *Stem Cell.* 15 (3) (1997) 180–189.
 - [33] C.W. Redman, I.L. Sargent, A.C. Staff, IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia? *Placenta* 35 (Suppl) (2014) S20–S25.
 - [34] T. Stallmach, G. Hebisch, P. Orban, X. Lu, Aberrant positioning of trophoblast and lymphocytes in the feto-maternal interface with pre-eclampsia, *Virchows Archiv: an international journal of pathology* 434 (3) (1999) 207–211.
 - [35] N. Bachmayer, R. Rafik Hamad, L. Liszka, K. Bremme, E. Sverremark-Ekstrom, Aberrant uterine natural killer (NK)-cell expression and altered placental and serum levels of the NK-cell promoting cytokine interleukin-12 in pre-eclampsia, *Am. J. Reprod. Immunol.* 56 (5–6) (2006) 292–301.
 - [36] J.R. Wilczyński, H. Tchorzewski, M. Banasik, E. Glowacka, A. Wiecek, P. Lewkowicz, A. Malinowski, M. Szpakowski, J. Wilczyński, Lymphocyte subset distribution and cytokine secretion in third trimester decidua in normal pregnancy and preeclampsia, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 109 (1) (2003) 8–15.
 - [37] P.J. Williams, J.N. Bulmer, R.F. Searle, B.A. Innes, S.C. Robson, Altered decidual leucocyte populations in the placental bed in pre-eclampsia and foetal growth restriction: a comparison with late normal pregnancy, *Reproduction* 138 (1) (2009) 177–184.
 - [38] I.P. Eide, T. Rolfseng, C.V. Isaksen, R. Mecsei, B. Roald, S. Lydersen, K.A. Salvesen, N.K. Harsem, R. Austgulen, Serious foetal growth restriction is associated with reduced proportions of natural killer cells in decidua basalis, *Virchows Archiv: an international journal of pathology* 448 (3) (2006) 269–276.
 - [39] S.E. Hiby, J.J. Walker, K.M. O'Shaughnessy, C.W. Redman, M. Carrington, J. Trowsdale, A. Moffett, Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success, *J. Exp. Med.* 200 (8) (2004) 957–965.
 - [40] J.E. Cartwright, G.S. Whitley, Strategies for investigating the maternal-fetal interface in the first trimester of pregnancy: what can we learn about pathology? *Placenta* 60 (2017) 145–149.
 - [41] A.E. Wallace, R. Fraser, S. Gurung, S.S. Goulwara, G.S. Whitley, A.P. Johnstone, J.E. Cartwright, Increased angiogenic factor secretion by decidual natural killer cells from pregnancies with high uterine artery resistance alters trophoblast function, *Hum. Reprod.* 29 (4) (2014) 652–660.
 - [42] R. Fraser, G.S. Whitley, B. Thilaganathan, J.E. Cartwright, Decidual natural killer cells regulate vessel stability: implications for impaired spiral artery remodelling, *J. Reprod. Immunol.* 110 (2015) 54–60.
 - [43] B.A. Croy, Z. Chen, A.P. Hofmann, E.M. Lord, A.L. Sedlacek, S.A. Gerber, Imaging of vascular development in early mouse decidua and its association with leukocytes and trophoblasts, *Biol. Reprod.* 87 (5) (2012) 125.
 - [44] A.A. Ashkar, J.P. Di Santo, B.A. Croy, Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy, *J. Exp. Med.* 192 (2) (2000) 259–270.
 - [45] Z. Chen, J. Zhang, K. Hatta, P.D. Lima, H. Yadi, F. Colucci, A.T. Yamada, B.A. Croy, DBA-lectin reactivity defines mouse uterine natural killer cell subsets with biased gene expression, *Biol. Reprod.* 87 (4) (2012) 81.
 - [46] C. Tayade, D. Hilchie, H. He, Y. Fang, L. Moons, P. Carmeliet, R.A. Foster, B.A. Croy, Genetic deletion of placenta growth factor in mice alters uterine NK cells, *J. Immunol.* 178 (7) (2007) 4267–4275.
 - [47] H. Yadi, S. Burke, Z. Madeja, M. Hemberger, A. Moffett, F. Colucci, Unique receptor repertoire in mouse uterine NK cells, *J. Immunol.* 181 (9) (2008) 6140–6147.
 - [48] M.J. Guimond, J.A. Luross, B. Wang, C. Terhorst, S. Danial, B.A. Croy, Absence of natural killer cells during murine pregnancy is associated with reproductive compromise in TgE26 mice, *Biol. Reprod.* 56 (1) (1997) 169–179.
 - [49] M.J. Guimond, B. Wang, B.A. Croy, Engraftment of bone marrow from severe combined immunodeficient (SCID) mice reverses the reproductive deficits in natural killer cell-deficient tg epsilon 26 mice, *J. Exp. Med.* 187 (2) (1998) 217–223.
 - [50] J.S. Hunt, L. Miller, D. Vassmer, B.A. Croy, Expression of the inducible nitric oxide synthase gene in mouse uterine leukocytes and potential relationships with uterine function during pregnancy, *Biol. Reprod.* 57 (4) (1997) 827–836.
 - [51] C. Wang, N. Umesaki, H. Nakamura, T. Tanaka, K. Nakatani, I. Sakaguchi, S. Ogita, K. Kaneda, Expression of vascular endothelial growth factor by granulated metrial gland cells in pregnant murine uteri, *Cell Tissue Res.* 300 (2) (2000) 285–293.
 - [52] F. Spaans, B.N. Melgert, C. Chiang, T. Borghuis, P.A. Klok, P. de Vos, H. van Goor, W.W. Bakker, M.M. Faas, Extracellular ATP decreases trophoblast invasion, spiral artery remodeling and immune cells in the mesometrial triangle in pregnant rats, *Placenta* 35 (8) (2014) 587–595.
 - [53] M.J. Soares, D. Chakraborty, M.A. Karim Rumi, T. Konno, S.J. Renaud, Rat placentation: an experimental model for investigating the hemochorial maternal-fetal interface, *Placenta* 33 (4) (2012) 233–243.
 - [54] M.M. Faas, P. de Vos, Uterine NK cells and macrophages in pregnancy, *Placenta* 56 (2017) 44–52.

- [55] D. Chakraborty, M.A. Rumi, T. Konno, M.J. Soares, Natural killer cells direct hemochorial placentation by regulating hypoxia-inducible factor dependent trophoblast lineage decisions, *Proc. Natl. Acad. Sci. U.S.A.* 108 (39) (2011) 16295–16300.
- [56] A.L. Winship, K. Koga, E. Menkhorst, M. Van Sinderen, K. Rainczuk, M. Nagai, C. Cuman, J. Yap, J.G. Zhang, D. Simmons, M.J. Young, E. Dimitriadis, Interleukin-11 alters placentation and causes preeclampsia features in mice, *Proc. Natl. Acad. Sci. U.S.A.* 112 (52) (2015) 15928–15933.
- [57] M. Golic, N. Haase, F. Herse, A. Wehner, L. Vercruyse, R. Pijnenborg, A. Balogh, P.C. Saether, E. Dissen, F.C. Luft, L. Przybyl, J.K. Park, P. Alnaes-Katjavivi, A.C. Staff, S. Verlohren, W. Henrich, D.N. Muller, R. Dechend, Natural killer cell reduction and uteroplacental vasculopathy, *Hypertension* 68 (4) (2016) 964–973.
- [58] S. Gordon, P.R. Taylor, Monocyte and macrophage heterogeneity, *Nat. Rev. Immunol.* 5 (12) (2005) 953–964.
- [59] C. Auffray, D. Fogg, M. Garfa, G. Elain, O. Join-Lambert, S. Kayal, S. Sarnacki, A. Cumano, G. Lauvau, F. Geissmann, Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior, *Science* 317 (5838) (2007) 666–670.
- [60] F. Porcheray, S. Viaud, A.C. Rimioli, C. Léone, B. Samah, N. Dereuddre-Bosquet, D. Dormont, G. Gras, Macrophage activation switching: an asset for the resolution of inflammation, *Clin. Exp. Immunol.* 142 (3) (2005) 481–489.
- [61] J.N. Bulmer, P.J. Williams, G.E. Lash, Immune cells in the placental bed, *Int. J. Dev. Biol.* 54 (2–3) (2010) 281–294.
- [62] J.N. Bulmer, L. Morrison, J.C. Smith, Expression of class II MHC gene products by macrophages in human uteroplacental tissue, *Immunology* 63 (4) (1988) 707–714.
- [63] U. Kämmerer, A.O. Eggert, M. Kapp, A.D. McLellan, T.B. Geijtenbeek, J. Dietl, Y. van Kooyk, E. Kämpgen, Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy, *Am. J. Pathol.* 162 (3) (2003) 887–896.
- [64] G. Laskarin, K. Cupurdija, V.S. Tokmadzic, D. Dorcic, J. Dupor, K. Juretic, N. Strbo, T.B. Crncic, F. Marchezi, P. Allavena, A. Mantovani, L. Randic, D. Rukavina, The presence of functional mannose receptor on macrophages at the maternal-fetal interface, *Hum. Reprod.* 20 (4) (2005) 1057–1066.
- [65] B.L. Houser, T. Tilburgs, J. Hill, M.L. Nicotra, J.L. Strominger, Two unique human decidual macrophage populations, *J. Immunol.* 186 (4) (2011) 2633–2642.
- [66] K. Cupurdija, D. Azzola, U. Hainz, A. Gratchev, A. Heitger, O. Takikawa, S. Goerd, R. Wintersteiger, G. Dohr, P. Sedlmayr, Macrophages of human first trimester decidua express markers associated to alternative activation, *Am. J. Reprod. Immunol.* 51 (2) (2004) 117–122.
- [67] D. Schonkeren, M.L. van der Hoorn, P. Khedoe, G. Swings, E. van Beelen, F. Claas, C. van Kooten, E. de Heer, S. Scherjon, Differential distribution and phenotype of decidual macrophages in preeclamptic versus control pregnancies, *Am. J. Pathol.* 178 (2) (2011) 709–717.
- [68] S. Engert, L. Rieger, M. Kapp, J.C. Becker, J. Dietl, U. Kämmerer, Profiling chemokines, cytokines and growth factors in human early pregnancy decidua by protein array, *Am. J. Reprod. Immunol.* 58 (2) (2007) 129–137.
- [69] C. Gustafsson, J. Mjösberg, A. Matussek, R. Geffers, L. Matthiesen, G. Berg, S. Sharma, J. Buer, J. Ernerudh, Gene expression profiling of human decidual macrophages: evidence for immunosuppressive phenotype, *PLoS One* 3 (4) (2008) e2078.
- [70] G.E. Lash, H. Pitman, H.L. Morgan, B.A. Innes, C.N. Agwu, J.N. Bulmer, Decidual macrophages: key regulators of vascular remodeling in human pregnancy, *J. Leukoc. Biol.* 100 (2) (2016) 315–325.
- [71] J. Svensson, M.C. Jenmalm, A. Matussek, R. Geffers, G. Berg, J. Ernerudh, Macrophages at the fetal-maternal interface express markers of alternative activation and are induced by M-CSF and IL-10, *J. Immunol.* 187 (7) (2011) 3671–3682.
- [72] V.M. Abrahams, Y.M. Kim, S.L. Straszewski, R. Romero, G. Mor, Macrophages and apoptotic cell clearance during pregnancy, *Am. J. Reprod. Immunol.* 51 (4) (2004) 275–282.
- [73] M. Piacentini, F. Autuori, Immunohistochemical localization of tissue transglutaminase and Bcl-2 in rat uterine tissues during embryo implantation and post-partum involution, *Differentiation* 57 (1) (1994) 51–61.
- [74] M.R. Bürk, C. Troeger, R. Brinkhaus, W. Holzgreve, S. Hahn, Severely reduced presence of tissue macrophages in the basal plate of pre-eclamptic placentae, *Placenta* 22 (4) (2001) 309–316.
- [75] F. Reister, H.G. Frank, J.C. Kingdom, W. Heyl, P. Kaufmann, W. Rath, B. Huppertz, Macrophage-induced apoptosis limits endovascular trophoblast invasion in the uterine wall of preeclamptic women, *Lab. Invest.* 81 (8) (2001) 1143–1152.
- [76] J.S. Kim, R. Romero, E. Cushenberry, Y.M. Kim, O. Erez, J.K. Nien, B.H. Yoon, J. Espinoza, C.J. Kim, Distribution of CD14+ and CD68+ macrophages in the placental bed and basal plate of women with preeclampsia and preterm labor, *Placenta* 28 (5–6) (2007) 571–576.
- [77] F. Reister, H.G. Frank, W. Heyl, G. Kosanke, B. Huppertz, W. Schröder, P. Kaufmann, W. Rath, The distribution of macrophages in spiral arteries of the placental bed in pre-eclampsia differs from that in healthy patients, *Placenta* 20 (2–3) (1999) 229–233.
- [78] M. Hayashi, K. Hoshimoto, T. Ohkura, N. Inaba, Increased levels of macrophage colony-stimulating factor in the placenta and blood in preeclampsia, *Am. J. Reprod. Immunol.* 47 (1) (2002) 19–24.
- [79] H. Katabuchi, S. Yih, T. Ohba, K. Matsui, K. Takahashi, M. Takeya, H. Okamura, Characterization of macrophages in the decidual atherosclerotic spiral artery with special reference to the cytology of foam cells, *Med. Electron. Microsc.* 36 (4) (2003) 253–262.
- [80] M. Haeger, M. Unander, B. Norder-Hansson, M. Tylman, A. Bengtsson, Complement, neutrophil, and macrophage activation in women with severe preeclampsia and the syndrome of hemolysis, elevated liver enzymes, and low platelet count, *Obstet. Gynecol.* 79 (1) (1992) 19–26.
- [81] D.F. Benyo, A. Smarason, C.W. Redman, C. Sims, K.P. Conrad, Expression of inflammatory cytokines in placentas from women with preeclampsia, *J. Clin. Endocrinol. Metab.* 86 (6) (2001) 2505–2512.
- [82] Y. Wang, S.W. Walsh, TNF alpha concentrations and mRNA expression are increased in preeclamptic placentas, *J. Reprod. Immunol.* 32 (2) (1996) 157–169.
- [83] C. Helige, H. Ahmmer, A. Hammer, B. Huppertz, H.G. Frank, G. Dohr, Trophoblastic invasion in vitro and in vivo: similarities and differences, *Hum. Reprod.* 23 (10) (2008) 2282–2291.
- [84] S.J. Renaud, L.M. Postovit, S.K. Macdonald-Goodfellow, G.T. McDonald, J.D. Caldwell, C.H. Graham, Activated macrophages inhibit human cytotrophoblast invasiveness in vitro, *Biol. Reprod.* 73 (2) (2005) 237–243.
- [85] S.J. Renaud, S.K. Macdonald-Goodfellow, C.H. Graham, Coordinated regulation of human trophoblast invasiveness by macrophages and interleukin 10, *Biol. Reprod.* 76 (3) (2007) 448–454.
- [86] Z.J. Pang, F.Q. Xing, Comparative study on the expression of cytokine-receptor genes in normal and preeclamptic human placentas using DNA microarrays, *J. Perinat. Med.* 31 (2) (2003) 153–162.
- [87] A. Hennessy, H.L. Pilmor, L.A. Simmons, D.M. Painter, A deficiency of placental IL-10 in preeclampsia, *J. Immunol.* 163 (6) (1999) 3491–3495.
- [88] D.T. Rein, M. Breidenbach, B. Hönscheid, U. Friebe-Hoffmann, H. Engel, U.J. Göhring, L. Uekermann, C.M. Kurbacher, T. Schönborn, Preeclamptic women are deficient of interleukin-10 as assessed by cytokine release of trophoblast cells in vitro, *Cytokine* 23 (4–5) (2003) 119–125.
- [89] R.J. Buckley, G.S. Whitley, I.E. Dumitriu, J.E. Cartwright, Macrophage polarisation affects their regulation of trophoblast behaviour, *Placenta* 47 (2016) 73–80.
- [90] J.R. Prins, M.M. Faas, B.N. Melgert, S. Huitema, A. Timmer, M.N. Hylkema, J.J. Erwich, Altered expression of immune-associated genes in first-trimester human decidua of pregnancies later complicated with hypertension or foetal growth restriction, *Placenta* 33 (5) (2012) 453–455.
- [91] Y. Xu, R. Romero, D. Miller, L. Kadam, T.N. Mial, O. Plazyo, V. Garcia-Flores, S.S. Hassan, Z. Xu, A.L. Tarca, S. Drewlo, N. Gomez-Lopez, An m1-like macrophage polarization in decidual tissue during spontaneous preterm labor that is attenuated by rosiglitazone treatment, *J. Immunol.* 196 (6) (2016) 2476–2491.
- [92] D.R. Tessier, S. Raha, A.C. Holloway, J. Yockell-Lievre, C. Tayade, A. Gruslin, Characterization of immune cells and cytokine localization in the rat uteroplacental unit mid- to late gestation, *J. Reprod. Immunol.* 110 (2015) 89–101.
- [93] N.C. Douglas, R.C. Zimmermann, Q.K. Tan, C.S. Sullivan-Pyke, M.V. Sauer, J.K. Kitajewski, C.J. Shawber, VEGFR-1 blockade disrupts peri-implantation decidual angiogenesis and macrophage recruitment, *Vasc. Cell* 6 (2014) 16.
- [94] O. Shynlova, T. Nedd-Roderique, Y. Li, A. Dorogin, T. Nguyen, S.J. Lye, Infiltration of myeloid cells into decidua is a critical early event in the labour cascade and post-partum uterine remodelling, *J. Cell Mol. Med.* 17 (2) (2013) 311–324.
- [95] T. Cotechini, M. Komisarenko, A. Sperou, S. Macdonald-Goodfellow, M.A. Adams, C.H. Graham, Inflammation in rat pregnancy inhibits spiral artery remodeling leading to fetal growth restriction and features of preeclampsia, *J. Exp. Med.* 211 (1) (2014) 165–179.
- [96] I. Mellman, Dendritic cells: master regulators of the immune response, *Cancer immunology research* 1 (3) (2013) 145–149.
- [97] U. Kammerer, M. Schoppert, A.D. McLellan, M. Kapp, H.I. Huppertz, E. Kämpgen, J. Dietl, Human decidua contains potent immunostimulatory CD83(+) dendritic cells, *Am. J. Pathol.* 157 (1) (2000) 159–169.
- [98] L. Rieger, A. Honig, M. Sutterlin, M. Kapp, J. Dietl, P. Ruck, U. Kammerer, Antigen-presenting cells in human endometrium during the menstrual cycle compared to early pregnancy, *J. Soc. Gynecol. Invest.* 11 (7) (2004) 488–493.
- [99] U. Kammerer, A.O. Eggert, M. Kapp, A.D. McLellan, T.B. Geijtenbeek, J. Dietl, Y. van Kooyk, E. Kämpgen, Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy, *Am. J. Pathol.* 162 (3) (2003) 887–896.
- [100] L. Gardner, A. Moffett, Dendritic cells in the human decidua, *Biol. Reprod.* 69 (4) (2003) 1438–1446.
- [101] D. Croxatto, P. Vacca, F. Canegallo, R. Conte, P.L. Venturini, L. Moretta, M.C. Mingari, Stromal cells from human decidua exert a strong inhibitory effect on NK cell function and dendritic cell differentiation, *PLoS One* 9 (2) (2014) e89006.
- [102] S. Miyazaki, H. Tsuda, M. Sakai, S. Hori, Y. Sasaki, T. Futatani, T. Miyawaki, S. Saito, Predominance of Th2-promoting dendritic cells in early human pregnancy decidua, *J. Leukoc. Biol.* 74 (4) (2003) 514–522.
- [103] P. Hsu, B. Santner-Nanan, J.E. Dahlstrom, M. Fadia, A. Chandra, M. Peek, R. Nanan, Altered decidual DC-SIGN+ antigen-presenting cells and impaired regulatory T-cell induction in preeclampsia, *Am. J. Pathol.* 181 (6) (2012) 2149–2160.
- [104] D.M. Andrews, A.A. Scalzo, W.M. Yokoyama, M.J. Smyth, M.A. Degli-Esposti, Functional interactions between dendritic cells and NK cells during viral infection, *Nat. Immunol.* 4 (2) (2003) 175–181.
- [105] G. Laskarin, A. Redzovic, Z. Rubesa, A. Mantovani, P. Allavena, H. Haller, I. Vlastelic, D. Rukavina, Decidual natural killer cell tuning by autologous dendritic cells, *Am. J. Reprod. Immunol.* 59 (5) (2008) 433–445.
- [106] P. Vacca, C. Cantoni, M. Vitale, C. Prato, F. Canegallo, D. Fenoglio, N. Ragni, L. Moretta, M.C. Mingari, Crosstalk between decidual NK and CD14+ myelomonocytic cells results in induction of Tregs and immunosuppression, *Proc. Natl. Acad. Sci. U.S.A.* 107 (26) (2010) 11918–11923.
- [107] S.J. Huang, C.P. Chen, F. Schatz, M. Rahman, V.M. Abrahams, C.J. Lockwood, Preeclampsia is associated with dendritic cell recruitment into the uterine decidua, *J. Pathol.* 214 (3) (2008) 328–336.
- [108] W. Zhang, Y. Zhou, Y. Ding, Lnc-DC mediates the over-maturation of decidual

- dendritic cells and induces the increase in Th1 cells in preeclampsia, *Am. J. Reprod. Immunol.* 77 (6) (2017).
- [109] A.H. Zarnani, S.M. Moazzeni, F. Shokri, M. Salehnia, M. Jeddi Tehrani, Analysis of endometrial myeloid and lymphoid dendritic cells during mouse estrous cycle, *J. Reprod. Immunol.* 71 (1) (2006) 28–40.
- [110] S.A. Robertson, V.J. Mau, K.P. Tremellen, R.F. Seamark, Role of high molecular weight seminal vesicle proteins in eliciting the uterine inflammatory response to semen in mice, *J. Reprod. Fertil.* 107 (2) (1996) 265–277.
- [111] M.K. Collins, C.S. Tay, A. Erlebacher, Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice, *J. Clin. Invest.* 119 (7) (2009) 2062–2073.
- [112] H.N. Ahmadabad, M. Salehnia, S. Saito, S.M. Moazzeni, Decidual soluble factors, through modulation of dendritic cells functions, determine the immune response patterns at the feto-maternal interface, *J. Reprod. Immunol.* 114 (2016) 10–17.
- [113] S. Miranda, S. Litwin, G. Barrientos, L. Szeredy, E. Chuluyan, J.S. Bartho, P.C. Arck, S.M. Blois, Dendritic cells therapy confers a protective microenvironment in murine pregnancy, *Scand. J. Immunol.* 64 (5) (2006) 493–499.
- [114] I. Tirado-Gonzalez, G. Barrientos, N. Freitag, T. Otto, V.L. Thijssen, P. Moschansky, P. von Kwiatkowski, B.F. Klapp, E. Winterhager, S. Bauersachs, S.M. Blois, Uterine NK cells are critical in shaping DC immunogenic functions compatible with pregnancy progression, *PLoS One* 7 (10) (2012) e46755.
- [115] V. Plaks, T. Birnberg, T. Berkutzi, S. Sela, A. BenYashar, V. Kalchenko, G. Mor, E. Keshet, N. Dekel, M. Neeman, S. Jung, Uterine DCs are crucial for decidual formation during embryo implantation in mice, *J. Clin. Invest.* 118 (12) (2008) 3954–3965.
- [116] G. Krey, P. Frank, V. Shaikly, G. Barrientos, R. Cordo-Russo, F. Ringel, P. Moschansky, I.V. Chernukhin, M. Metodiev, N. Fernandez, B.F. Klapp, P.C. Arck, S.M. Blois, In vivo dendritic cell depletion reduces breeding efficiency, affecting implantation and early placental development in mice, *J. Mol. Med.* 86 (9) (2008) 999–1011.
- [117] G. Barrientos, I. Tirado-Gonzalez, B.F. Klapp, K. Karimi, P.C. Arck, M.G. Garcia, S.M. Blois, The impact of dendritic cells on angiogenic responses at the fetal-maternal interface, *J. Reprod. Immunol.* 83 (1–2) (2009) 85–94.
- [118] S.M. Blois, N. Freitag, I. Tirado-Gonzalez, S.B. Cheng, M.M. Heimesaat, S. Bereswill, M. Rose, M.L. Conrad, G. Barrientos, S. Sharma, NK cell-derived IL-10 is critical for DC-NK cell dialogue at the maternal-fetal interface, *Sci. Rep.* 7 (1) (2017) 2189.
- [119] S.M. Blois, G. Barrientos, M.G. Garcia, A.S. Orsal, M. Tometten, R.I. Cordo-Russo, B.F. Klapp, A. Santoni, N. Fernandez, P. Terness, P.C. Arck, Interaction between dendritic cells and natural killer cells during pregnancy in mice, *J. Mol. Med.* 86 (7) (2008) 837–852.
- [120] D.D. Metcalfe, D. Baram, Y.A. Mekori, Mast cells, *Physiol. Rev.* 77 (4) (1997) 1033–1079.
- [121] K. Woidacki, F. Jensen, A.C. Zenclussen, Mast cells as novel mediators of reproductive processes, *Front. Immunol.* 4 (2013) 29.
- [122] E. Sivridis, A. Giatromanolaki, N. Agnantis, P. Anastasiadis, Mast cell distribution and density in the normal uterus—metachromatic staining using lectins, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 98 (1) (2001) 109–113.
- [123] L. Drudy, B. Sheppard, J. Bonnar, Mast cells in the normal uterus and in dysfunctional uterine bleeding, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 39 (3) (1991) 193–201.
- [124] F.M. Menzies, C.A. Higgins, M.C. Shepherd, R.J. Nibbs, S.M. Nelson, Mast cells reside in myometrium and cervix, but are dispensable in mice for successful pregnancy and labor, *Immunol. Cell Biol.* 90 (3) (2012) 321–329.
- [125] R.E. Garfield, A.M. Irani, L.B. Schwartz, E. Bytautiene, R. Romero, Structural and functional comparison of mast cells in the pregnant versus nonpregnant human uterus, *Am. J. Obstet. Gynecol.* 194 (1) (2006) 261–267.
- [126] N. Meyer, K. Woidacki, M. Knofler, G. Meinhardt, D. Nowak, P. Velicky, J. Pollheimer, A.C. Zenclussen, Chymase-producing cells of the innate immune system are required for decidual vascular remodeling and fetal growth, *Sci. Rep.* 7 (2017) 45106.
- [127] D. Szukiewicz, A. Szukiewicz, D. Maslinska, M. Gujski, P. Poppe, J. Mazurek-Kantor, Mast cell number, histamine concentration and placental vascular response to histamine in preeclampsia, *Inflamm. Res.: official journal of the European Histamine Research Society.* 48 (Suppl 1) (1999) S39–S40 [et al.].
- [128] R. Mitani, K. Maeda, R. Fukui, S. Endo, Y. Saijo, K. Shinohara, M. Kamada, M. Irahara, S. Yamano, Y. Nakaya, T. Aono, Production of human mast cell chymase in human myometrium and placenta in cases of normal pregnancy and preeclampsia, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 101 (2) (2002) 155–160.
- [129] G. Szewczyk, M. Pyzlak, J. Klimkiewicz, W. Smiertka, M. Miedzinska-Maciejewski, D. Szukiewicz, Mast cells and histamine: do they influence placental vascular network and development in preeclampsia? *Mediat. Inflamm.* 2012 (2012) 307189.
- [130] K. Woidacki, N. Meyer, A. Schumacher, A. Goldschmidt, M. Maurer, A.C. Zenclussen, Transfer of regulatory T cells into abortion-prone mice promotes the expansion of uterine mast cells and normalizes early pregnancy angiogenesis, *Sci. Rep.* 5 (2015) 13938.
- [131] K. Woidacki, M. Popovic, M. Metz, A. Schumacher, N. Linzke, A. Teles, F. Poirier, S. Fest, F. Jensen, G.A. Rabinovich, M. Maurer, A.C. Zenclussen, Mast cells rescue implantation defects caused by c-kit deficiency, *Cell Death Dis.* 4 (2013) e462.
- [132] J. Varayoud, J.G. Ramos, V.L. Bosquiazio, M. Munoz-de-Toro, E.H. Luque, Mast cells degranulation affects angiogenesis in the rat uterine cervix during pregnancy, *Reproduction* 127 (3) (2004) 379–387.
- [133] V.L. Bosquiazio, J.G. Ramos, J. Varayoud, M. Munoz-de-Toro, E.H. Luque, Mast cell degranulation in rat uterine cervix during pregnancy correlates with expression of vascular endothelial growth factor mRNA and angiogenesis, *Reproduction* 133 (5) (2007) 1045–1055.
- [134] N. Meyer, K. Woidacki, M. Maurer, A.C. Zenclussen, Safeguarding of fetal growth by mast cells and natural killer cells: deficiency of one is counterbalanced by the other, *Front. Immunol.* 8 (2017) 711.
- [135] N. Meyer, T. Schuler, A.C. Zenclussen, Simultaneous ablation of uterine natural killer cells and uterine mast cells in mice leads to poor vascularization and abnormal Doppler measurements that compromise fetal well-being, *Front. Immunol.* 8 (2017) 1913.